Elsevier Editorial System(tm) for Clinical Neurophysiology
Manuscript Draft

Manuscript Number: CLINPH-D-13-7209R3

Title: Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy

Article Type: Full Length Article

Section/Category: Epilepsy

Keywords: Intracranial EEG, invasive recordings, seizure onset, epilepsy surgery, surgical outcome.

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*Abstract

ABSTRACT

Objective: To investigate if intracranial EEG patterns at seizure onset can predict surgical outcome.

Methods: Ictal onset patterns from intracranial EEG were analysed in 373 electro-clinical seizures and subclinical seizures from 69 patients. Seizure onset patterns were classified as: a) Diffuse electrodecremental (DEE); b) Focal fast activity (FA); c) Simultaneous onset of fast activity and diffuse electrodecremental event (FA-DEE); d) Spikes; e) Spike-wave activity; f) Sharp waves; g) Alpha activity; h) Delta activity. Presence of preceding epileptiform discharge (PED) was also studied. Engel and ILAE surgical outcome scales were used.

Results: The mean follow-up period was 42.1 months (SD=30.1). Fast activity was the most common seizure onset pattern seen (33%), followed by (FA-DEE) (20%), DEE (19%), spike-wave activity (12%), sharp-waves (6%), alpha activity (6%), delta activity (3%) and spikes (1%). Preceding epileptiform discharges were present in 75% of patients. FA was associated with favourable outcome (p=0.0083) whereas DEE was associated with poor outcome (p=0.0025). A widespread PED was not associated with poor outcome (p=0.9559). There was no clear association between seizure onset pattern and specific pathology, except possibly between sharp/spike waves and mesial temporal sclerosis.

Conclusions: FA activity is associated with favourable outcome. DEE at onset was associated with poor surgical outcome. Widespread/bilateralPEDs were not associated with poor or good outcome.

Significance: FA appears to be the best marker for the epileptogenic zone. Surgery should be contemplated with caution if DEE is the first ictal change. However, a widespread/bilateral PED at onset is common and should not discourage surgery.

Key words: Intracranial EEG, invasive recordings, seizure onset, epilepsy surgery, surgical outcome.

Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy

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Disclosure: None of the authors has any sources of support regarding this study, or any conflict of interest to disclose.

Funding: The National Secretariat for Higher Education, Science, Technology and Innovation of Ecuador (SENESCYT) funded this work as part of a PhD thesis.

Highlights:

1. Focal fast activity at onset was associated with favourable outcome.
2. Diffuse electrodecremental event at onset was associated with poor outcome
3. A preceding focal, widespread or bilateral epileptiform discharge was not associated with either favourable or poor outcome.

ABSTRACT

Objective: To investigate if intracranial EEG patterns at seizure onset can predict surgical outcome.

Methods: Ictal onset patterns from intracranial EEG were analysed in 373 electro-clinical seizures and subclinical seizures from 69 patients. Seizure onset patterns were classified as: a) Diffuse electrodecremental (DEE); b) Focal fast activity (FA); c) Simultaneous onset of fast activity and diffuse electrodecremental event (FA-DEE); d) Spikes; e) Spike-wave activity; f) Sharp waves; g) Alpha activity; h) Delta activity. Presence of preceding epileptiform discharge (PED) was also studied. Engel and ILAE surgical outcome scales were used.

Results: The mean follow-up period was 42.1 months (SD=30.1). Fast activity was the most common seizure onset pattern seen (33%), followed by (FA-DEE) (20%), DEE (19%), spike-wave activity (12%), sharp-waves (6%), alpha activity (6%), delta activity (3%) and spikes (1%). Preceding epileptiform discharges were present in 75% of patients. FA was associated with favourable outcome (p=0.0083) whereas DEE was associated with poor outcome (p=0.0025). A widespread PED was not associated with poor outcome (p=0.9559). There was no clear association between seizure onset pattern and specific pathology, except possibly between sharp/spike waves and mesial temporal sclerosis.

Conclusions: FA activity is associated with favourable outcome. DEE at onset was associated with poor surgical outcome. Widespread/bilateralPEDs were not associated with poor or good outcome.

Significance: FA appears to be the best marker for the epileptogenic zone. Surgery should be contemplated with caution if DEE is the first ictal change. However, a widespread/bilateral PED at onset is common and should not discourage surgery.

Key words: Intracranial EEG, invasive recordings, seizure onset, epilepsy surgery, surgical outcome.

INTRODUCTION

Resective surgery can achieve seizure freedom in 40 to 70% of patients with drug-resistant epilepsy (Wiebe et al. , 2001, de Tisi et al. , 2011, Kumar et al. , 2013). Successful outcome of surgery depends on accurate identification of the epileptogenic zone (Engel et al. , 1993, Luders et al. , 2006, Gelziniene et al. , 2008, Jette et al. , 2013). At present, a variety of non-invasive techniques are initially used to identify the epileptogenic zone, including interictal and ictal scalp electroencephalography (Adachi et al. , 1998, Alarcon et al. , 2001, Alarcon et al. , 2012b), neuroimaging (Koutroumanidis et al. , 2004, Duncan, 2010) and neuropsychology (Akanuma et al. , 2003). However, in approximately 25% of patients assessed for surgery, non-invasive techniques are non-localising or non-concordant, and assessment with intracranial electrodes may be necessary to identify the epileptogenic zone (Alarcon et al. , 2006).

The EEG recorded with intracranial electrodes shows larger amplitude and less muscle artefacts than the scalp EEG. In addition, intracranial recordings show a wider variety of interictal and ictal abnormalities than the scalp EEG (Fernandez Torre et al. , 1999b, Kissani et al. , 2001) not necessarily restricted to the ictal onset zone (Alarcon et al. , 1995, Fernandez Torre et al. , 1999a, Kissani et al. , 2001). Interictal slowing of the background activity occur at or around the area of seizure onset in around 80% of patients assessed with chronic intracranial recordings (Valentin et al. , 2014). In 40-100% of patients, spontaneous interictal epileptiform discharges occur independently at the seizure onset zone and elsewhere, including contralateral cortex (Alarcon et al. , 1994, Fernandez Torre et al. , 1999b).

Despite the presence of interictal abnormalities, the interpretation of chronic intracranial recordings still heavily relies on the identification of the ictal onset zone, i.e. the area where seizures start on intracranial recordings. A difficulty arises from the fact that the onset of focal seizures can be associated with a variety of EEG patterns, which are not necessarily focal in distribution (Alarcon et al. , 1995). Approximately two thirds of focal seizures start with a run of focal fast activity, sharp waves, spikes or slow waves lasting for a few seconds (Alarcon et al. , 1995). However, in one third of seizures, focal changes are preceded by more widespread patterns, such as a diffuse attenuation of the background activity (diffuse electrodecremental event or DEE) (Alarcon et al. , 1995). In many human recordings, these sustained ictal changes are immediately preceded by a single epileptiform discharge (preceding epileptiform discharge, or PED), which can show a widespread or bilateral distribution and is associated with a prominent slow wave. A similar phenomenon described as "leading spike" has been reported in 15 children with epileptic spasms (Asano et al. , 2005). Altough PEDs are transitory phenomena resembling interictal activity, their association with seizures is obvious, as they consistently occur immediately preceding the onset of the more sustained ictal patterns described above. The physiological and clinical significance of such widespread changes at seizure onset in focal epilepsy are unclear.

To simplify wording throughout the paper, the ictal onset patterns which typically last for several seconds (DEE and runs of focal fast activity, sharp waves, spikes or slow waves) will be generically designated as "sustained ictal onset patterns"

(SIOP). PEDs can precede any type of SIOP and consequently will be analysed separately. The term "seizure onset patterns" will include SIOPs and PEDs.

To the best of our knowledge, the prognostic significance of PEDs has not been reported in focal epilepsies. Its removal is associated with favourable outcome in infantile spasms (Asano et al. , 2005). Several authors have studied the value of intracranial SIOPs to predict surgical outcome (Lieb et al. , 1986, Spencer et al. , 1992, Alarcon et al. , 1995, Jung et al. , 1999, Kutsy et al. , 1999, Lee et al. , 2000, Zaatreh et al. , 2003, Wetjen et al. , 2009, Holtkamp et al. , 2012, Dolezalova et al. , 2013). These studies suggest that the presence of focal fast activity at seizure onset appears to be associated with seizure relief after resective surgery. However, the prognostic value of the more widespread SIOPs is unclear. DEE is one of the most common SIOP, occurring in as many as 60% of patients assessed with intracranial electrodes (Alarcon et al. , 1995, Zaatreh et al. , 2003, Perucca et al. , 2013) and is the first SIOP in about a third of seizures recorded with intracranial electrodes (Alarcon et al., 1995). Early studies on a very limited number of cases suggested that the presence of DEE does not significantly affect surgical outcome (Alarcon et al. , 1995). Unfortunately, larger studies on the prognostic value of ictal onset patterns have not usually included DEE in their analysis (Spencer et al. , 1992, Lee et al. , 2000, Wetjen et al. , 2009, Holtkamp et al. , 2012, Park et al. , 2012). One publication suggested that the presence of DEE may be associated with poor surgical outcome in temporal lobe epilepsy (Dolezalova et al. , 2013), and one abstract has reported that the same may occur in extratemporal epilepsy (Zaatreh et al. , 2003).

In the present work, we study the prognostic value with regard to seizure control and pathology of the following intracranial seizure onset patterns: PED, DEE, runs of focal fast activity (FA), spikes, sharp waves, alpha or slow activity. We report a series of 69 consecutive patients undergoing resective surgery for the treatment of epilepsy, the largest study published to date, including temporal and extratemporal patients. We also analyse the prognostic significance of widespread and bilateral PEDs. Preliminary results have been published in abstract form (Jimenez-Jimenez et al. , 2013).

METHODS

Patients

The study initially included all 74 patients who underwent cortical resective surgery for the treatment of epilepsy after assessment with intracranial electrodes implanted at King's College Hospital between 08th of November 1999 and the 23th of December 2010 and had postsurgical follow-up of 12 months or longer. The following patients were excluded: a) Patients who had no seizures during telemetry (1 patient), b) Patients who underwent hemispherectomy for the treatment of Rasmussen Disease (1 patient), c) Patients being assessed for reoperation after failure of the first operation (3 patients; in two patients after multiple subpial transection had failed and in one patient having removal of hypothalamic hamartoma after a frontal resection had failed). This left a total of 69 patients to be included the study. Ictal recordings from all 69 patients were reviewed.

Under UK regulations, no NHS Research Ethics Committee approval was required under section 6 of the Governance Arrangements for Research Ethics Committees (September 2011). The Neuroscience Audit Committee at King's College Hospital has approved this study.

Electrode placement

The type, number and location of the electrodes were determined by the suspected location of the ictal onset region, according to non-invasive evaluation: clinical history, scalp EEG recordings obtained with the Maudsley system (Fernandez

Torre et al. , 1999b, Alarcon et al. , 2001, Kissani et al. , 2001), neuropsychology (Akanuma et al. , 2003) and neuroimaging. All patients with normal neuroimaging were assessed with intracranial electrodes. The selection criteria and implantation procedures have been described in detail elsewhere (Alarcon et al. , 2006, Alarcon, 2012).

Subdural electrodes: Subdural electrodes consisted of strips and mats (AdTech Medical Instruments Corp., WI, USA). Each strip consisted of a single row of 4 to 8 platinum disk electrodes spaced at 10 mm between centres. The disks were embedded in a 0.7 mm thick polyurethane strip which overlapped the edges leaving a diameter of 2.3 mm exposed, and recessed approximately 0.1 mm from the surface plane. Mats contained rectangular arrays of 12, 16, 20, 32 or 64 similar platinum electrodes with 10 mm centre-to-centre distances within rows.

Intracerebral (depth) electrodes: Multicontact flexible bundles of depth electrodes (AdTech Medical Instruments Corp., WI, USA) were implanted stereotactically under MRI guidance. The electrode bundles contained 8 or 10 cylindrical 2.3 mm long platinum contacts separated by 5 mm between centres of adjacent electrodes of the same bundle.

The position of the electrodes was confirmed with post-implantation CT or MRI.

Electroencephalographic recordings

Recording of intracranial EEG started when the patient had recovered from electrode implantation, usually 24-48 hours after surgery. Cable telemetry with up

to 64 recording channels was used for data acquisition with simultaneous video monitoring. In 31 patients, the Telefactor Beehive-Beekeeper system (Astro-Med, RI, USA) was used. Data were digitized at 200 Hz and band pass filtered (high pass cut-off frequency at 0.3 Hz and low pass cut-off frequency at 70 Hz). The system input range was 2 mV and data were digitized with a 12 bit analog-to-digital converter (amplitude resolution of 0.488 μV). In the remaining 38 patients, a Medelec-Profile system was used (Medelec, Oxford Instruments, United Kingdom). Data were digitized at 256 Hz and band pass filtered (0.05-70 Hz). The input range was 10 mV and data were digitized with a 22 bit analog-to-digital converter (an amplitude resolution of 0.153 μV). Data were recorded as common reference to Pz or to an intracranial electrode, and displayed in a variety of montages including various scalp, intracranial and average common references to identify the most inactive reference for review in each patient. When common average reference was used, channels showing large spikes or artifacts or responses were removed from the average. Ictal files were generated by selecting EEG recordings that started at least 5 minutes before clinical or electroencephalographic seizure onset.

Seizure onset analysis

This study included all 373 seizures (323 electro-clinical and 50 subclinical seizures) from all 69 patients. Seizure onset was determined by visual analysis of the pruned ictal files of intracranial EEG recordings. The SIOP was the first sustained ictal change observed at the beginning of seizures. The SIOPs seen on the EEG were visually classified into: fast activity (FA), spike-and-wave activity, rhythmic sharp waves, alpha activity, delta activity, theta activity, and diffuse electrodecrement event (DEE). The categorization of these EEG patterns was

carried out jointly by DJJ and GA while blind to surgical outcome and according to the recommendations of the International Federation of Societies for Clinical Neurophysiology (Noachtar et al. , 1999). When FA and DEE started within one second, this was classified as different pattern designated as FA-DEE. Consequently, each seizure was characterised by a single SIOP: FA, DEE, FA-DEE, spike-and-wave activity, rhythmic sharp waves, alpha activity, delta activity, or theta activity. The presence, location, laterality, duration, extension and frequency (number of cycles per second, if applicable) of each pattern were recorded. The location, laterality duration and extension of FA-DEE patterns were defined by the fast activity.

The presence, topography and extension of PED were also noted. PEDs were considered: a) Focal: if they were recorded from 3 or less neighboring subdural electrodes, or from 5 or less neighboring depth electrodes; b) Widespread if they were recorded from more than 3 neighboring subdural electrodes, or from more than 5 neighboring depth electrodes, in the same hemisphere; and c) Bilateral if they were recorded from electrodes in both hemispheres.

In order to correlate seizure onset patterns with surgical outcome, a pooled database was developed that summarised features from each patient's seizures into a single entry. Patients were divided into those with a single seizure onset type and those with more than one seizure onset type. Among the latter, the most common seizure type was considered for analysis. For quantitative variables (e.g. frequency of fast activity in Hz), the mean of all patient's seizures was used.

Surgical Procedures

Surgery included temporal, frontal, parietal, insular and occipital resections. Tissue was removed and pathology studies performed. En-bloc temporal lobectomies followed an anatomically standardised surgical techniques (Alarcon, 2009). En bloc temporal lobectomy was undertaken at the Maudsley and King's College Hospitals as originally described by Falconer (Falconer, 1971), later modified to achieve a more complete removal of the hippocampus by use of the principles described by Spencer (Spencer et al. , 1984). In effect, between 5.5 cm and 6.5 cm of temporal lobe was removed. In the dominant hemisphere, usually the left, all superior temporal gyrus except the anterior 2 cm was spared. Such a resection would have included at least 50% of the amygdala and 2–3 cm of parahippocampal gyrus and hippocampus. Electrocorticographic intraoperative recordings were carried out and the extent of the resection was occasionally modified according to electrocorticographic findings (Alarcon et al. , 1997). In extratemporal procedures, chronic intracranial EEG recordings were used for guiding the craniotomy in order to remove the seizure onset zone. Intraoperative electrocorticographic recordings were used to further tailor the resection to remove regions showing pathological slowing and epileptiform discharges (Ferrier et al. , 2001). Structural lesions shown on imaging were removed unless functional mapping suggested a significant risk of functional deficits. Post-operative imaging was performed in those patients where surgery failed.

Neuropathology

Neuropathological examination of the resected specimens was carried out according to the departmental protocol outlined previously (Kumar et al. , 2013).

Surgical outcome

Surgical outcome with regard to seizure control was determined at regular postoperative follow up assessments. Surgical outcome was coded according to both the ILAE and Engel surgical outcome classifications (Engel et al. , 1993, Wieser et al. , 2001). Surgical outcome at the longest follow-up available was used for each patient. For statistical analysis, only Engel classification was used. Grade I was considered as "good outcome" and grades II, III or IV as "poor outcome".

Statistical analysis

Univariate analysis: Two-tailed χ^2 testing with one degree of freedom and with Yate's correction was used to compare the proportion of patients with favourable outcome between the groups of patients showing each seizure onset pattern or presence/absence of PED. Existence of significant differences was assumed if $p<0.05$. Analysis was carried out with Graphpad.
(www.graphpad.com/quickcalcs/contingency1.cfm).

Multivariate analysis

Backward stepwise multiple logistic regression analysis were undertaken using SPSS for MAC OSX version 21. Surgical outcome was the dependent variable and the following most common SIOPs were used as independent covariates: DEE, FA, FA-DEE and spike wave activity. PEDs cohexisted with SIOP and thereore were not

considered as independent covariates. Consequently, PEDs were not included in the model. Similarly, the location of seizure onset was not incorporated in the multivariate analysis.

RESULTS

Patients

Among all 69 patients, 31 (45%) patients were female and 38 (55%) were male. The mean age at onset of epilepsy was 10.73 years (SD=9.07). The average age at resection was 31.8 years (SD=13.0). The mean follow-up period was 42.15 months (SD=30.1). Table 1 summarises patients' details. Fifty-one patients (73.9%) underwent temporal lobe resections, 13 (18.8%) had frontal resections, two (2.9%) patients underwent parietal resections, two (2.9%) had occipital resections, and one patient underwent an insular resection. The most common pathology found after resection was mesial temporal sclerosis, which was present in 28 patients (40.6%), followed by focal cortical dysplasia which was present in 12 patients (17.4%), 6 patients (8.7%) revealed dysembryoplastic neuroepithelial tumor, two patients (2.9%) showed heterotopia, and non-specific changes were seen in 9 patients (13.0%).

Intracranial electrodes

Among all 69 patients, 28 patients (40.6%) had subdural strips only, 17 patients (24.6%) had depth electrodes only, 15 patients (21.7%) had a combination of subdural mat and strip electrodes, 4 patients (5.8%) had mat electrodes only, 4 patients (5.8%) had a combination of depth and subdural strips electrodes and one patient (1.4%) had depth and mat electrodes.

Regarding electrode coverage, 38 patients (55.1%) had electrodes restricted to the temporal lobes, one patient (1.4%) had electrodes restricted to the frontal lobes,

17 patients (24.6%) had electrodes in the temporal and frontal lobes, 5 patients (7.2%) had electrodes covering temporal, frontal and parietal lobes, 4 patients (5.8%) had electrodes in temporal and occipital lobes, 3 patients (4.3%) had electrodes in the temporal and parietal lobes, and one patient (1.4%) had electrodes covering the frontal and parietal lobes. Fifty patients (72.5%) had electrodes implanted bilaterally and 19 patients (27.5%) had unilateral electrodes.

Topography of resections and surgical outcome

Table 2 shows the relation between the location of resection and surgical outcome in all 69 patients. Temporal lobe resections showed the highest rate of improvement after surgery. Among the larger group of 51 temporal resections, 25 showed focal medial temporal seizure onset, 8 showed a regional onset involving medial temporal structures, and 18 showed lateral temporal onset.

Seizure onset patterns

A total of 373 seizures from the 69 patients were analysed. Representative examples of each seizure onset pattern found are shown in figures 1-5. The most common SIOP was FA, which was seen in 23 patients (33.3%) with a mean frequency of 25.5Hz (SD=21). FA-DEE was the seizure onset pattern in 14 patients (20.3%) with a mean of 16.5Hz (SD=24.4), DEE in 13 patients (18.9%), spike-wave activity in 8 (11.6%) patients (mean frequency = 3.5Hz; SD=1.07), sharp-waves in 4 (5.8%) patients (mean frequency = 4.7Hz; SD=0.96), alpha in 4 (5.8%) patients (mean frequency = 9.2Hz; SD=0.957), delta activity in two (2.9%) patients (mean frequency=1Hz; SD=1.4) and runs of spikes in one (1.4%) patient at a frequency of 4 Hz.

Fifty-six patients presented a single SIOP type and 13 had different SIOPs in different seizures. Among the latter, eight patients showed all seizures arising from the same structure with different seizure onset patterns, and five patients showed seizures arising independently from different structures within the same lobe. No significant differences in outcome were found between the 56 patients with a single seizure onset type and the 13 patients with more than one seizure onset type.

PEDs were present in 52 patients (75.4%), were focal in 9 patients (13.0%), widespread in 32 patients (47.0%) and bilateral in 11 patients (16.0%). When PEDs were present, they involved an average of 8 contacts (SD±8.43) more than the focal seizure onset patterns.

Among the 51 temporal patients, the SIOP was FA in 17 (33.3%) patients, FA-DEE in 10 (19.6%), DEE in 7 (13.7%), spike-wave activity in 7 (13.7%) patients, sharp waves in 4 (7.8%), alpha activity in 3 (5.9%), delta activity in 2 (3.9%) and rhythmic spikes in one (2%) patient. Among the 13 frontal patients, the SIOP was FA in three 3 (23.1%) patients, FA-DEE in 3 (23.1%), DEE in 6 (46.2%), and spike wave activity in one (7.7%) patient. Among the two parietal patients, the SIOPs were FA in one patient and alpha activity in another. Among the two occipital patients, FA was the SIOP in one patient and FA-DEE in another. The only insular patient showed FA as SIOP.

Among the 51 temporal patients, PEDs were present in 37 (72.5%), were focal in 8 patients (15.7%), widespread in 23 patients (45.1%) and bilateral in 6 (11.8%).

Among the 18 extratemporal patients, PEDs were present in 15 (83.3%), were focal in 1 patient (5.6%), widespread in 9 patients (50%) and bilateral in 5 (27.8%).

Prognostic value of seizure onset patterns

Table 3 shows the relation between surgical outcome, SIOPs and presence of PEDs in all resections and in temporal resections. Data for extratemporal resections can be obtained by subtracting the data for temporal resections from the data for all resections. Among all patients, FA was the SIOP that showed the highest proportion of patients with Engel Grade I, accounting for 17 (73.9%) of the 23 patients, with only 6 (27.1%) presenting grades II-IV. Interestingly, when FA appeared at the same time as DEE, the proportion of Engel grade I decreased to 43%. On the other hand, we found that only 1 patient of 13 presenting DEE as the SIOP showed Engel Grade I whereas 12 (92%) showed poor outcome (grades II-IV). Among all 69 patients, 52 patients presented PED immediately before the seizure onset pattern. Interestingly, among the 11 patients with bilateral PEDs, 46% enjoyed favourable outcome.

Univariate statistical analysis: Two by two contingency tables were constructed to estimate the association between surgical outcome and different pairs of seizure onset patterns. This was carried out within the following three groups: all patients, temporal patients and extratemporal patients. The following comparisons were perfomed within each group:

a) FA versus any other SIOP;

b) FA versus DEE;

c) FA or FA-DEE versus absence of FA;

d) PED versus absence of PED;

e) Widespread or bilateral PED versus absence of widespread or bilateral PED;

f) PED and FA versus PED and any SIOP other than FA;

g) FA-DEE versus DEE;

h) DEE versus any other SIOP;

i) FA versus FA-DEE.

The interested reader can carry out any other comparison by choosing the appropriate cells in table 3.

Table 4 shows the 2x2 contingency tables with trends or significant associations between Engel outcome scale and seizure onset patterns in each patient group. In all 69 patients, FA showed better surgical outcome than other patterns, either when occurring on its own ($p=0.0083$) or in association with DEE ($p=0.039$). The better outcome associated with FA seizure onset is preserved when PEDs are present ($p=0.0081$). In contrast, DEE appears to be a predictor of poor surgical outcome when compared with FA ($p=0.0005$) or with any other seizure onset pattern ($p=0.0025$).

Among temporal resections, FA onset patterns showed better surgical outcome when compared to DEE ($p<0.0389$) (table 3). In addition, there is a trend towards an association between DEE and poorer outcome when compared with any other seizure onset pattern ($p=0.0721$).

Among extratemporal resections, patients with FA enjoyed better surgical outcome than those with seizures starting with other patterns (p=0.0263), and specifically with DEE (p=0.0192). In addition, there is a trend towards an association between DEE and poorer outcome when compared with any other seizure onset pattern (p=0.0601).

Multiple logistic regression

The following covariates were used for the logistic regression model: DEE, FA, FA-DEE and spike wave activity (Model $\chi 2$ =18,764, 3 df, p=0.00, Goodness of fit=29,482). Patients showing DEE were associated with a greater risk of failure to obtain Engel class I outcome compared with those not showing DEE (b=-3,584, SE=1,323, p=0.007).

Pathology

Table 5 shows the cross tabulation between seizure onset patterns and neuropathological findings for the 69 patients. Mesial temporal sclerosis and focal cortical dysplasia were the most common pathologies, accounting for 58% of patients. There was no clear association between seizure onset patterns and specific pathology, except possibly between sharp/spike waves and mesial temporal sclerosis. In the present study, FA was the most common SIOP, occurring in all pathological entities.

DISCUSSION

The purpose of this study is to estimate the prognostic value of the seizure onset pattern to predict seizure control and pathology after epilepsy surgery. We found that FA was associated with favourable surgical outcome, whereas DEE was associated with poor surgical outcome. The presence or topographic extension of PEDs was not correlated with outcome. There is no clear association between pathology and seizure onset pattern.

Clinical relevance

FA was the most common SIOP in temporal and extratemporal epilepsies and its presence was associated with favourable surgical outcome. This result is in concordance to previous studies (Lieb et al. , 1986, Spencer et al. , 1992, Alarcon et al. , 1995, Jung et al. , 1999, Kutsy et al. , 1999, Lee et al. , 2000, Wetjen et al. , 2009, Holtkamp et al. , 2012, Dolezalova et al. , 2013). These replicated observations support the notion that fast activity at seizure onset truly reflects in-situ generation of epileptic seizures.

In addition, more widespread patterns were also common. DEE was observed at seizure onset in 39% of patients, either in isolation (19%) or associated with fast activity (20%). DEE was associated with poor surgical outcome. Consequently, when discussing surgical outcome with patients, caution may be required if DEE is the SIOP. The prognostic significance of FA-DEE pattern appears to be in between that of FA and that of DEE.

PEDs were very common, present in 75.4% of patients, and among these, PEDs were widespread or bilateral in 63%. It would be difficult to consider PEDs as interictal activity, as they tend to be larger and more diffuse than interictal discharges, and occur immediately before each seizure, suggesting that they are involved in seizure initiation. Interestingly, their presence and topographic extension does not seem to affect surgical outcome. More specifically, the presence of a bilateral or widespread epileptiform discharge immediately preceding a seizure does not imply that the seizure is generalised, and should not necessarily preclude surgery.

With the exception of sharp/spike wave activity and mesial temporal sclerosis, there was not a clear association between seizure onset patterns and specific pathology, in concordance with previous reports in smaller series (Mathern et al. , 1995, Perucca et al. , 2014). This suggests that the mechanisms of epileptogenesis may be, to a degree, independent of the underlying pathology.

Statistics

An interesting finding is that DEE appears to have a prognostic value of its own, independently of FA. Apart from the comparison between FA and DEE, the most significant differences are found between DEE and any other SIOP (p=0.0025, table 3, and results from multiple logistic regression), suggesting that DEE has value of its own, independent of FA.

In contrast to DEE, our study failed to demonstrate a prognostic value for PED. There is no difference in outcome between those with PED and those without; or

between those with widespread or bilateral PED and those without widespread or bilateral PED. However, there is a difference between those with PED and FA and those with PED and any SIOP other than FA, probably due to the prognostic value of FA.

Pathophysiological implications

In our study, FA, DEE and FA-DEE were the most common SIOPs. The association between favourable postsurgical outcome and FA at seizure onset suggests that FA is a reliable preoperative biomarker of the epileptogenic zone. The present clinical study is limited to the standard EEG frequency band, below 70 Hz, which was used in routine clinical recordings during the period of recruitment. The clinical use of higher frequencies up to 600 Hz and beyond is presently under evaluation (Jirsch et al. , 2006, Jacobs et al. , 2008, Koehling et al. , 2011, Buzsaki et al. , 2012).

Recordings were obtained from different brain areas and electrode types, which may have influenced the incidence of SIOPs. Indeed, DEE was more common in frontal patients (46%), which may explain the poorer outcome observed in frontal epilepsies (Kumar et al. , 2013).

At the moment, the mechanisms of DEE and their relation to surgical outcome are not fully understood. It might be presumed that where the first detected SIOP is generalized, seizure onset is either diffuse or occurs at a site that has not been implanted, and that surgical outcome will consequently be poor, as suggested by our study. In principle, DEE can be explained by neuronal de-synchronisation or decrease in neuronal activity. To our knowledge, the mechanisms whereby the

initiation of focal seizures can be associated with such widespread changes in neuronal activity are unknown.

The physiological significance of PEDs is also puzzling. PEDs share similar morphology to interictal epileptiform discharges, with a sharp element followed by a prominent slow wave. The slow waves of interictal epileptiform discharges are associated with a period of inhibition lasting for several hundreds of milliseconds (Keller et al., 2010, Alarcon et al., 2012a). Likewise, the prominent slow wave associated with PEDs may be dominated by neuronal inhibition. Such inhibition is activated during spontaneous epileptiform discharges, and also by electrical stimulation of most cortical regions (Alarcon et al. , 2012a), suggesting a generic and broadly distributed mechanism for both. It is possible that a rebound increase in neuronal firing occurring after a period of widespread cortical inhibition might be responsible for excessive neuronal synchronisation resulting in seizures. The reasons why PEDs are widespread or bilateral in as many as 61% of patients are unclear, but may be due to the ubiquity of generic inhibitory mechanisms which are extensively found throughout the cortex and beyond (Alarcon et al. , 1990, Alarcon et al. , 2012a).

Limitations

The main limitation of the study is the heterogeneity of the patient population and methodology used. The series includes different epilepsy and seizure types, studied with subdural and depth electrodes, with various durations of telemetry. In some conditions, the numbers are small for statistical analysis (e.g., some SIOPs, parietal and occipital resections). However, due to the large number of patients

studied, in many subgroups (e.g., FA, DEE, FA-DEE, temporal and frontal resections) the number of patients is sufficient for correlation with outcome. Automatic analysis was difficult due to the enormous variety in the morphology of SIOPs, which drove the study towards more subjective visual analysis by human experts.

Conclusion

In the present paper, we characterise the incidence and prognostic value of focal, widespread and bilateral PEDs. FA, FA-DEE, DEE and PED are the most common SIOPs. The presence of FA as SIOP was associated with favourable surgical outcome, whereas DEE was associated with poor surgical outcome. Presence or topographic extension of PEDs was not correlated with good or poor outcome. There is no clear association between pathology and seizure onset patterns.

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Figure 1.

Example of FA seizure onset pattern in a patient with a 20-electrode mat over the left parietal lobe, a 10-electrode depth bundle along the left sylvian fisure, two 8-electrode subtemporal strips (parietal and subtemporal) and a 4-electrode strips over the occipital lobe, shown in common average reference. Note fast activity at 16 Hz arising at electrode 2 of the depth electrode. Mat = sylvian mat; DSyl = sylvian depth electrode; LsT = left subtemporal strip; LO = left occipital strip; LP = left parietal strip; ECG = electrocardiogram. For each strip and for the depth electrode bundle, electrode 1 is the farthest from the insertion site and 8 is the closest. For the mat, electrode 1 is at the anterior and superior corner.

Figure 2.

Example of seizure onset pattern consisting of sharpened delta activity in a patient with three 8-contact sudural strips (bilateral subtemporal strips and one right occipital strip), shown in common average reference. Note seizure onset with sharpened delta activity at electrodes 3-4 of the right subtempoal strip. RsT = Rigth subtemporal strip; ROc = Right occipital strip; LsT = Left suptemporal strip. For each strip, electrode 1 is furthest from the insertion burr hole.

Figure 3.

Example of seizure onset pattern consisting of FA-DEE activity in a patient with a right parietal 4-contact strip, an 8-contact strip implanted parallel to the right central fissure and reaching lateral temporal cortex, an 8-contact prasagittal strip covering the superior aspect of the right frontal and parietal lobes, two 4-contact centro-medial strips implanted bilaterally and two 8-contact anterior frontal strips implanted bilaterally reaching orbital cortices. The record is displayed with common average reference. Note fast activity restricted to electrodes 1-2 of the right centrotemporal strip starting simultaneously with a diffuse electrodecremental event involving all the electrodes of the right centro-temporal and superior frontal strips. There is PED involving largely the same contacts as the decrement. ROrb = right orbital 8-contact strip; RSF = right superior frontal/parietal 8-contact strip; RcT = right centro temporal 8-contact strip; RCM = right centro medial 4-contact strip; LOrb = left orbital 8-contact strip; LCM = left centro medial 4-contact strip. For each strip, electrodes 1 is the farthest from the insertion site and 8 is the closest

Figure 4

Example of seizure onset pattern consisting of spike-wave activity in a patient with bilateral subtemporal strips (anterior, mid and posterior on the right, and anterior and posterior on the left). The record is displayed with common average reference. Note seizure onset with spike-wave activity involving most electrodes of the right anterior subtempoal strip and the deepest electrodes of the right mid temporal strip. RaT = Right anterior temporal strip; RmT = Right medial temporal strip; RpT = Right posterior temporal strip; LpT = left posterior temporal strip; LaT = left anterior temporal strip. For each strip, electrode 1 is farthest from the insertion burr hole.

Figure 5

Example of seizure onset pattern consisting of DEE in a patient with a 64-electrode mat applied over the right parietal lobe and one 8-contact subdural strip implanted in the right frontal lobe. The record is displayed with common average reference. Note seizure onset starting with DEE involving all electrodes. RF = Right frontal. For each strip, electrode 1 is farthest from the insertion burr hole. For the mat, electrode 1 is at the anterior and superior corner.

Figure 1

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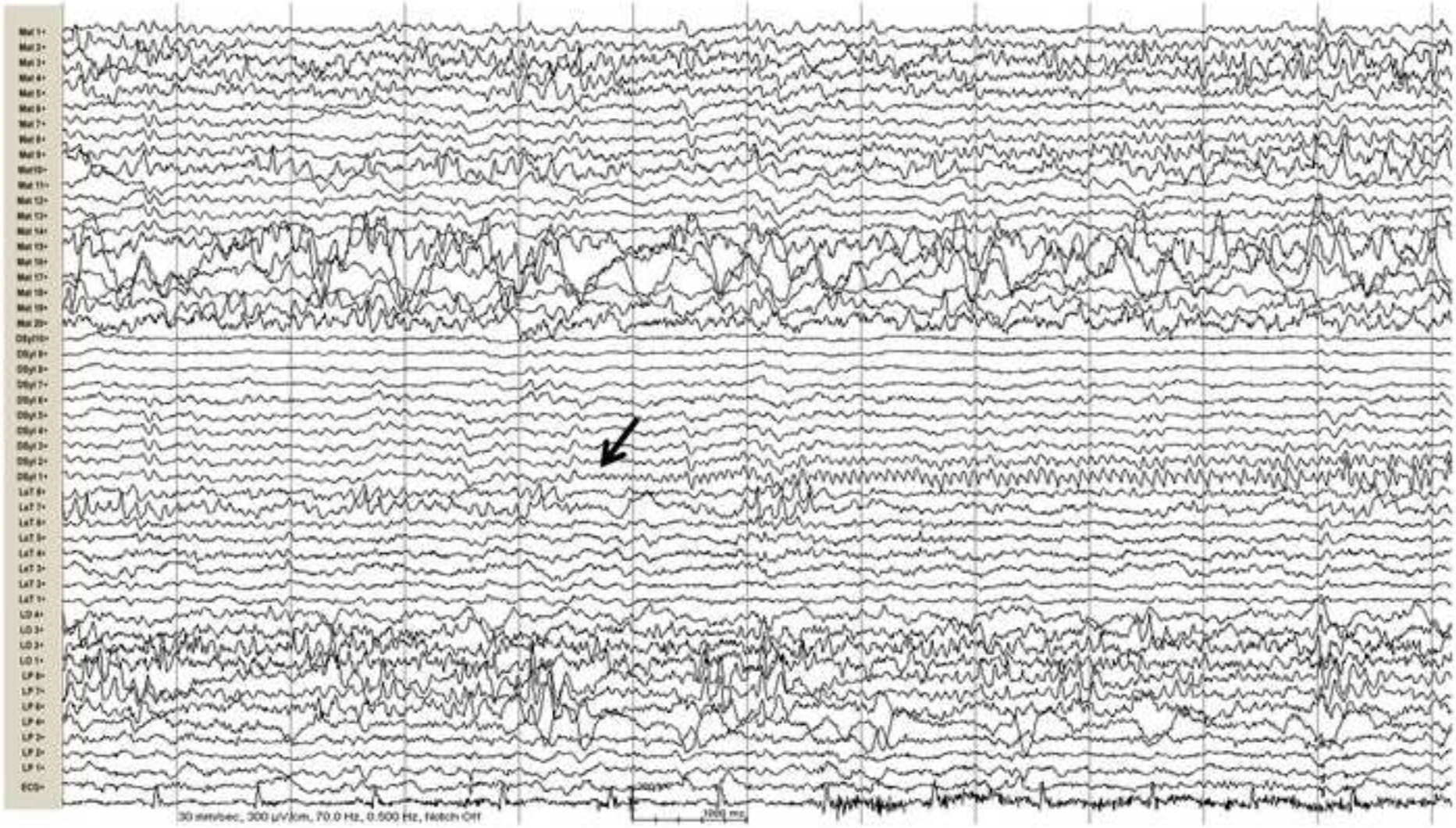

Figure 2

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Figure 3

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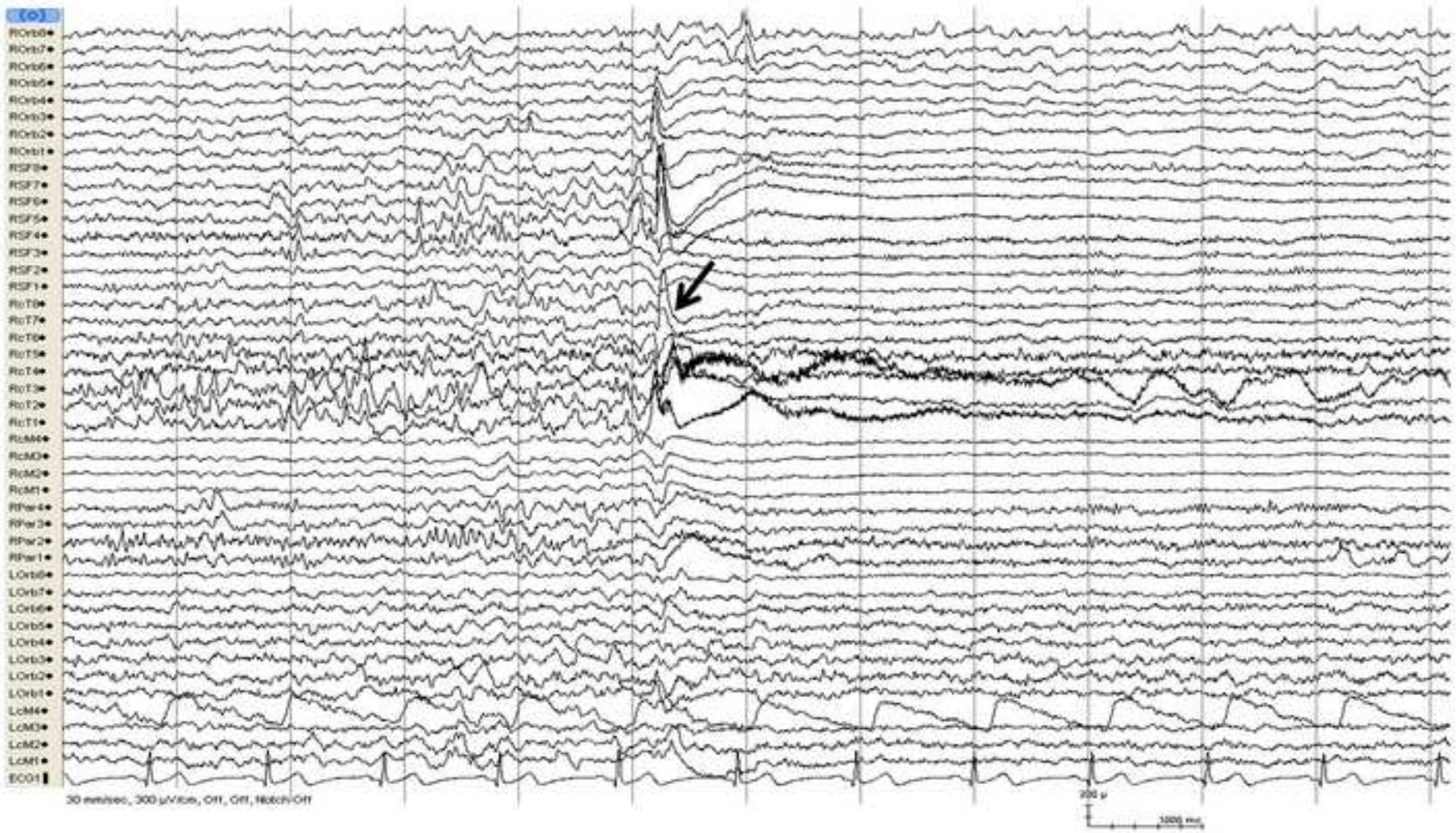

Figure 4

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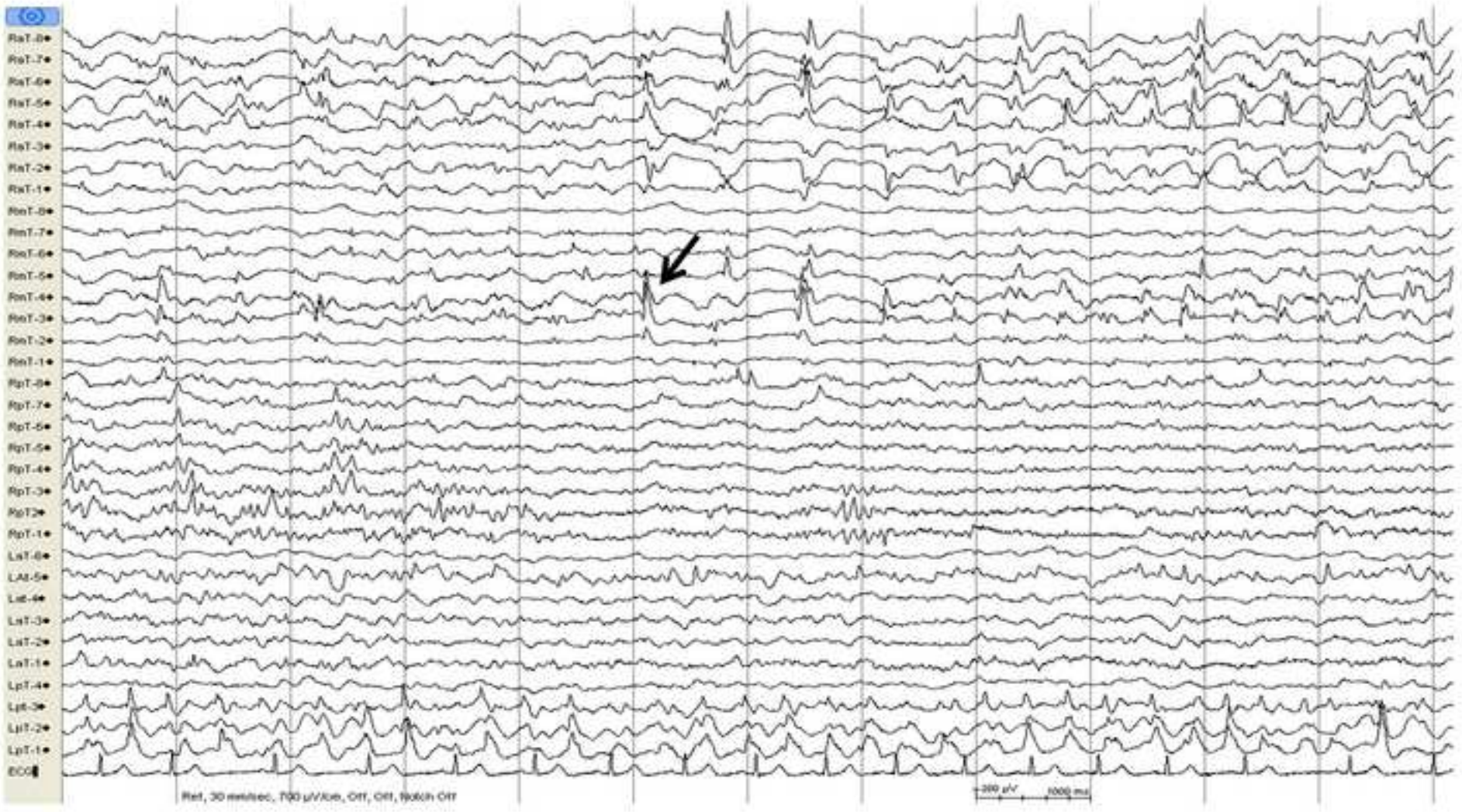

Figure 5

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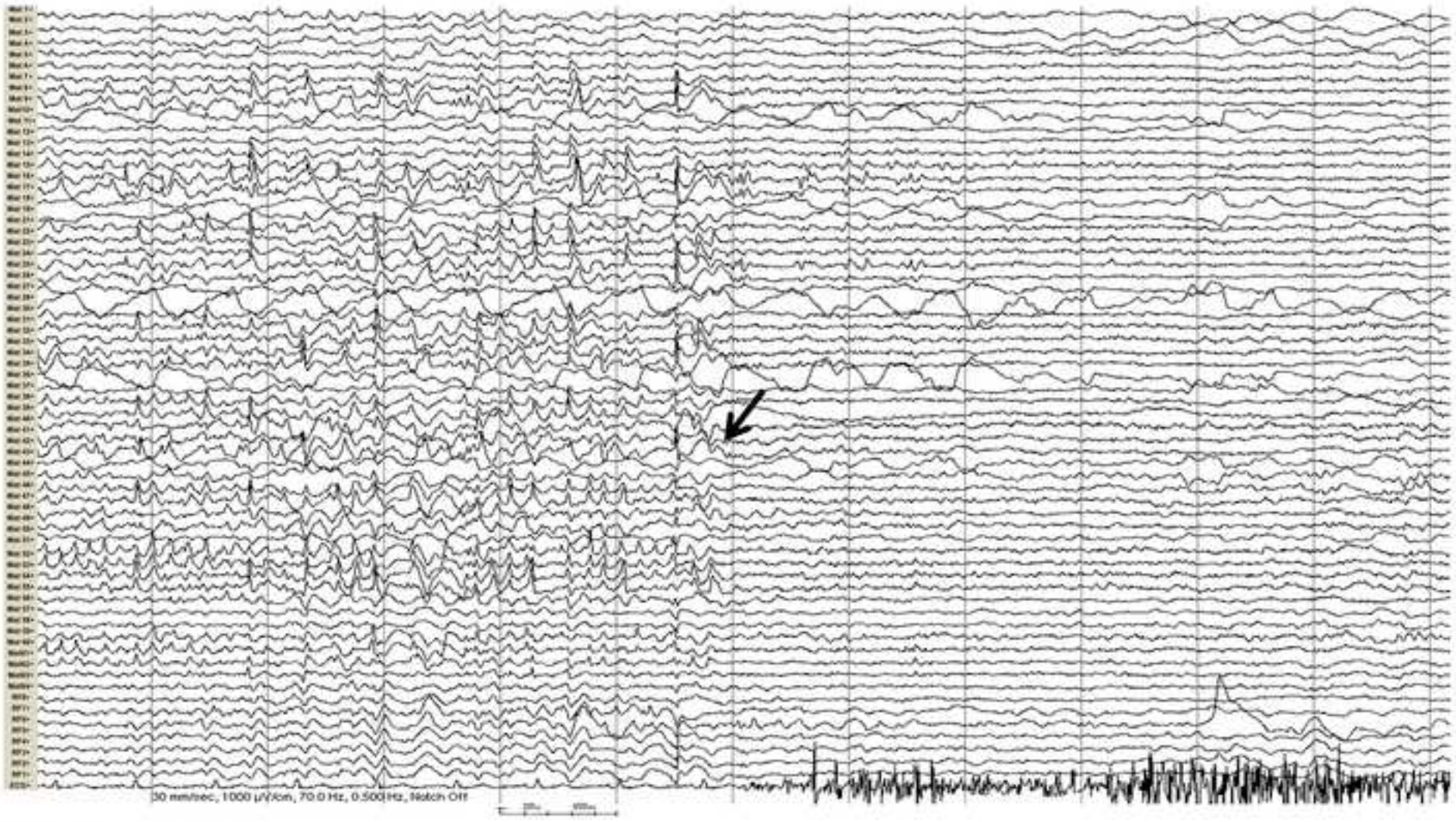

Table 1

Table 1. Summary of all 69 studied patients

Patient	Telemetry duration (days)	Number of Seizures	Electrodes Type	SIOP	PED	Pathology	Resected Lobe	Engel
1	12	2	Subdural	DEE	Widespread	MTS	Temporal	2
2	7	5	Mat and Subdural	FA	Focal	MTS	Temporal	1
3	20	7	Mat and Subdural	Alpha	Not present	ASTRO	Temporal	3
4	14	2	Depth	FA-DEE	Widespread	Tumour	Temporal	3
5	5	2	Depth	FA-DEE	Widespread	No changes	Temporal	1
6	20	7	Depth	DEE	Bilateral	FCD	Temporal	4
7	4	5	Subdural	Alpha	Widespread	MTS	Temporal	1
8	13	4	Depth	FA	Focal	MTS	Temporal	1
9	14	4	Depth	FA-DEE	Bilateral	Heterotopia	Temporal	2
10	8	4	Subdural	FA	Not present	Tumour	Temporal	4
11	3	3	Subdural	FA	Widespread	MTS	Temporal	1
12	11	4	Depth	Sharp-waves	Widespread	MTS	Temporal	1
13	4	6	Subdural	FA	Focal	MTS	Temporal	2
14	13	1	Subdural	FA	Not present	MTS	Temporal	2
15	6	3	Subdural	Delta	Not present	MTS	Temporal	2
16	6	3	Depth	FA	Widespread	MTS	Temporal	1
17	14	3	Mat	DEE	Widespread	EPNS	Temporal	2
18	12	9	Mat	FA	Widespread	FCD	Parietal	1
19	6	1	Mat	FA-DEE	Widespread	FCD	Frontal	4
20	8	3	Subdural	FA-DEE	Widespread	No changes	Temporal	3
21	9	3	Subdural	FA-DEE	Widespread	MTS	Temporal	3
22	5	2	Subdural	Spike-wave	Not present	MTS	Temporal	1
23	5	13	Depth	FA-DEE	Bilateral	FCD	Frontal	1
24	7	7	Depth	FA	Focal	DNET	Temporal	1
25	8	8	Mat and Subdural	Spike-wave	Not present	FCD	Temporal	3
26	10	4	Subdural	Sharp waves	Widespread	No changes	Temporal	1
27	20	2	Depth	FA	Widespread	Heterotopia	Occipital	1
28	13	2	Subdural	FA	Focal	No changes	Temporal	1
29	10	4	Mat and Subdural	Spike-wave	Not present	MTS	Temporal	1
30	3	3	Subdural	Spike-wave	Bilateral	DNET	Temporal	1
31	7	4	Subdural	Alpha	Widespread	MTS	Temporal	1
32	4	12	Mat	DEE	Widespread	FCD	Frontal	4
33	8	5	Subdural	Sharp waves	Not present	MTS	Temporal	3
34	7	5	Subdural	FA	Not present	MTS	Temporal	1
35	8	8	Depth and Subdural	Spike-wave	Focal	FCD	Frontal	2
36	13	4	Subdural	DEE	Widespread	No changes	Temporal	3
37	9	4	Depth	FA-DEE	Bilateral	MTS	Temporal	2
38	12	6	Depth	FA	Not present	FCD	Insula	3
39	7	5	Depth and Mat	FA	Not present	DNET	Frontal	1
40	3	10	Subdural	FA	Not present	MTS	Temporal	3
41	8	5	Subdural	DEE	Widespread	MTS	Temporal	1
42	3	14	Mat and Subdural	DEE	Widespread	No changes	Temporal	3
43	7	7	Subdural	Spike-wave	Focal	MTS	Temporal	1
44	5	6	Mat and Subdural	DEE	Not present	Heterotopia	Frontal	3
45	6	7	Mat and Subdural	DEE	Widespread	No changes	Frontal	3
46	6	2	Mat and Subdural	DEE	Widespread	ASTRO	Frontal	3
47	12	4	Subdural	FA	Not present	DNET	Temporal	1
48	16	1	Depth	FA	Not present	No changes	Temporal	1
49	9	5	Depth	Spike-wave	Bilateral	MTS	Temporal	1
50	5	4	Subdural	DEE	Bilateral	ASTRO	Frontal	4
51	5	5	Depth and Subdural	FA-DEE	Bilateral	DNET	Occipital	1
52	6	3	Mat and Subdural	Sharp waves	Not present	MTS	Temporal	2
53	7	6	Subdural	FA	Widespread	No changes	Temporal	1
54	11	3	Mat and Subdural	FA-DEE	Widespread	No changes	Temporal	1
55	6	13	Depth	Delta	Focal	MTS	Temporal	3
56	9	11	Subdural	Spike-wave	Widespread	MTS	Temporal	1
57	4	14	Depth and Subdural	Alpha	Widespread	FCD	Parietal	3
58	7	5	Subdural	FA	Focal	No changes	Temporal	1
59	16	5	Subdural	FA-DEE	Widespread	MTS	Temporal	1
60	3	19	Depth	FA-DEE	Bilateral	No changes	Frontal	3
61	4	5	Subdural	DEE	Widespread	DNET	Temporal	3

Patient	Telemetry duration (days)	Number of Seizures	Electrodes Type	SIOP	PED	Pathology	Resected Lobe	Engel
62	7	11	Depth and Subdural	Spikes	Bilateral	MTS	Temporal	3
63	7	8	Depth	FA	Not present	MTS	Temporal	1
64	8	3	Mat and Subdural	DEE	Widespread	FCD	Frontal	3
65	5	3	Mat and Subdural	FA-DEE	Widespread	MTS	Temporal	1
66	14	3	Mat and Subdural	FA-DEE	Widespread	No changes	Temporal	3
67	9	4	Mat and Subdural	FA	Widespread	FCD	Frontal	1
68	9	4	Subdural	FA	Bilateral	FCD	Frontal	1
69	9	4	Mat and Subdural	FA	Widespread	PIC	Temporal	4

§DNET= Dysembryoplastic neuroepithelial tumor
FDC= Focal cortical dysplasia
MTS= Mesial Temporal Sclerosis
PIC= Perinatal Ischemic Cyst

Table 2

Table 2. Number of patients with each outcome grade according to resection lobe for Engel and ILAE outcome classifications.

Engel Class	I	II	III	IV
	%	%	%	%
Temporal resections (n=51)	52.9	15.7	25.5	5.9
Frontal resections (n=13)	30.8	7.7	38.5	23.1
Parietal resections (n=2)	50.0	0.0	50.0	0.0
Occipital resections (n=2)	100	0.0	0.0	0.0
Insular resections (n=1)	0.0	0.0	100	0.0
TOTAL (n=69)	49.3	13.0	29.0	8.7

ILAE Class	1	2	3	4	5	6
	%	%	%	%	%	%
Temporalresections (n=51)	41.2	11.8	15.7	25.5	5.9	0.0
Frontal resections (n=13)	23.1	7.7	15.4	30.8	23.1	0.0
Parietal resections (n=2)	50.0	0.0	0.0	50.0	0.0	0.0
Occipital resections (n=2)	50.0	0.0	50.0	0.0	0.0	0.0
Insular resections (n=1)	0.0	0.0	0.0	100	0.0	0.0
TOTAL (n=69)	37.7	10.1	15.9	27.5	8.7	0

Table 3

Table 3. Relation between seizure onset pattern and Engel surgical outcome in temporal and extratemporal resections.

	I	II	III	IV
ALL RESECTIONS	**%**	**%**	**%**	**%**
SIOP				
FA (n=23)	73.9	8.7	8.7	8.7
FA-DEE (n=14)	42.9	14.3	35.7	7.1
DEE (n=13)	7.7	15.4	53.8	23.1
Spike-wave activity (n=8)	75.0	12.5	12.5	0.0
Alpha (n=4)	50.0	0.0	50.0	0.0
Sharp-waves (n=4)	50.0	25.0	25.0	0.0
Delta (n=2)	0.0	50.0	50.0	0.0
Spikes (n=1)	0.0	0.0	100	0.0
TOTAL (n=69)	49.3	13.0	29.0	8.7
PED				
Focal PEDs (n=9)	66.7	22.2	11.1	0.0
Widespread PEDs (n=32)	50.0	6.3	34.4	9.4
Bilateral PEDs (n=11)	45.5	18.2	18.2	18.2
TOTAL (n=52)	51.9	11.5	26.9	9.6
TEMPORAL RESECTIONS	**%**	**%**	**%**	**%**
SIOP				
FA (n=17)	70.6	11.8	5.9	11.8
FA-DEE (n=10)	40.0	20.0	40.0	0.0
DEE (n=7)	14.3	28.6	42.9	14.3
Spike-wave activity (n=7)	85.7	0.0	14.3	0.0
Alpha (n=3)	66.7	0.0	33.3	0.0
Sharp-waves (n=4)	50.0	25.0	25.0	0.0
Delta (n=2)	0.0	50.0	50.0	0.0
Spikes (n=1)	0.0	0.0	100	0.0
TOTAL (n=51)	52.9	15.7	25.5	5.9
PED				
Focal PEDs (n=8)	75.0	12.5	12.5	0.0
Widespread PEDs (n=23)	56.5	8.7	30.4	4.3
Bilateral PEDs (n=6)	33.3	33.3	16.7	16.7
TOTAL (n=37)	56.8	13.5	24.3	5.4

FA = fast activity
FA-DEE = fast activity and diffuse electrodecremental event
DEE = diffuse electrodecremental event
PED = preceding epileptiform discharge

Table 4

Table 4. Relation between seizure onset pattern and surgical outcome. Contincency tables showing trends or signficant associations. χ^2 = two tailed Chi squared test with Yates correction (1 degree of freedom); * = significant difference

SEIZURE ONSET PATTERNS COMPARED	Good	Poor	Statistic	P
ALL PATIENTS				
FA Any other SIOP	17 17	6 29	χ^2=6.95	0.0083 *
FA DEE	17 1	6 12	χ^2= 12.04	0.0005*
FA or FA-DEE Absence of FA	23 11	14 21	χ^2= 4.247	0.0393*
PED and FA PED and any SIOP other than FA	12 15	2 23	χ^2= 7.009	0.0081*
DEE Any other SIOP	1 33	12 23	χ^2= 9.126	0.0025*
TEMPORAL PATIENTS				
FA DEE	12 1	5 6	χ^2= 4.266	0.0389*
DEE Any other SIOP	1 26	6 18	χ^2= 3.234	0.0721
EXTRATEMPORAL PATIENTS				
FA Any other SIOP	5 2	1 10	χ^2= 4.938	0.0263*
FA DEE	5 0	1 6	χ^2= 5.486	0.0192*
FA or FA-DEE Absence of FA	7 0	3 8	χ^2= 6.455	0.0111*
DEE Any other SIOP	0 7	6 5	χ^2= 3.536	0.0601

Good = good surgical outcome (grade I of Engel classification)
Poor = poor surgical outcome (grades II, III or IV of Engel classification)
FA = fast activity
DEE = diffuse electrodecremental event
FA-DEE = fast activity and simultaneous diffuse electrodecremental event
PED = preceding epileptiform discharge.

Table 5

Table 5. Cross tabulation seizure onset pattern and Pathology.

Subpopulation	Astrocytosis	DNET	FCD	MTS	No Changes	Perinatal Ischemic Cyst	Tumour
SIOP	%	%	%	%	%	%	%
Alpha (n=4)	25.0	0.0	25.0	50.0	0.0	0.0	0.0
Decrement (n=13)	15.4	15.4	23.1	15.4	23.1	0.0	7.7
Delta (n=2)	0.0	0.0	0.0	100.0	0.0	0.0	0.0
Fast (n=23)	0.0	13.0	17.4	39.1	17.4	4.3	8.7
FA-DEE (n=14)	0.0	7.1	14.3	28.6	35.7	0.0	14.3
Sharp-wave (n=4)	0.0	0.0	0.0	75.0	25.0	0.0	0.0
Spike-wave (n=8)	0.0	12.5	25.0	62.5	0.0	0.0	0.0
Spikes (n=1)	0.0	0.0	0.0	100.0	0.0	0.0	0.0
TOTAL (n=69)	**4.3**	**10.1**	**17.4**	**40.6**	**18.8**	**1.4**	**7.2**
PED							
Focal PEDs (n=9)	0.0	11.1	11.1	55.6	11.1	0.0	11.1
WidespreadPEDs (n=32)	0.0	3.1	18.8	34.4	21.9	3.1	21.9
Bilateral PEDs (n=11)	9.1	18.2	27.3	27.3	0.0	0.0	18.2
TOTAL (n=52)	**1.9**	**7.7**	**19.2**	**36.5**	**15.4**	**1.9**	**19.2**

DNET= Dysembryoplastic neuroepithelial tumor
FDC= Focal cortical dysplasia
MTS= Mesial Temporal Sclerosis